REMARKS

Applicants are submitting this amendment supplementally to their amendment of 17 December 2007 in order to reflect the changes in the claims as discussed in the telephone interview between Examiners Mear and Prouty and the Applicants' undersigned attorney. The interview took place on 16 January 2008. Applicants and their undersigned attorney wish to thank Examiners Mear and Prouty for granting the telephone interview and for providing helpful suggestions for amending the claims to remove indefinite expressions and to better distinguish over the cited prior art.

Antecedent basis for the amendments to claims 1, 14 and 26 and for new claim 28 may be found in the specification on page 5, line 14 through page 6, line 21; and in Example 1 on pages 23 through 26. Thus claims 1 through 8, 14 through 20, and 26 through 28 are now in the application and are presented for examination.

Examiner Prouty indicated that she believed that the claims last presented were much clearer than the claims as originally presented, but that she still wanted additional changes in independent claims 1, 14 and 26. Examiner Prouty indicated that the amended claims 1, 14 and 26, now presented, were more in line with the wording that she believed was appropriate to clearly define what the Applicants regarded as their invention. The independent claim 1 now presented make it clear that the recombinant nucleic acids according to the present invention

include at least one serine biosynthesis gene and a nucleotide sequence encoding L-serine dehydratase, which is partially deleted or is mutated, or fragments of the nucleotide sequence encoding L-serine dehydratase, flanking the 5' and the 3' end of said nucleotide sequence, encoding L-serine dehydratase to permit complete removal of said nucleotide sequence, including L-serine dehydratase by homologous recombination, and which is expressed to a lesser degree than the expression of the naturally occurring SEQ ID NO: 1 or is not expressed at all. Claims 14 and 26 have been amended to make it clear that the endogenous nucleotide sequence encoding L-serine dehydratase no longer encodes a protein with L-serine dehydratase activity.

Examiner Prouty questioned whether the Applicants are the first to isolate the L-serine dehydratase gene from Corynebacterium glutamicum and cited a Gen Bank Reference from NAKAGAWA published 5 June 2002. Examiner Meah sent the undersigned attorneys a copy of this reference by telefax and Applicants now enclose a copy of NAKAGAWA et al to complete te record.

Examiner Prouty indicated that NAKAGAWA is citable prior art, either per se or in combination with KUBOTA and LOVINGER et al, already of record. Thus Examiner Prouty indicated that NAKAGAWA may be anticipatory of claim 1 and perhaps NAKAGAWA in combination with KUBOTA and/or LOVINGER et al provides a strong argument for the obviousness of all claims.

Applicants agree only that NAKAGAWA was the first to publish the serine dehydratase sequence of Corynebacterium glutamicum. This is as assumed identical to serine deaminase, a term used also for the same enzyme. However, NAKAGAWA did not isolate the serine dehydratase gene. NAKAGAWA determined the genome sequence of C. glutamicum, and among the 3009 genes found, NAKAGAWA named one of the genes serine deaminase. NAKAGAWA neither cloned that gene, nor identified its function in an enzyme assay, nor used its sequence to derive an L-serine producer. Rather NAKAGAWA's denomination as a L-serine dehydratase (or deaminase) was only a result of comparison with a computer with other known sequences. Because of this there was no teaching about the function of the gene and the corresponding protein because real function can only be identified by experiments testing the activity of the enzyme encoded by the gene, as in an enzyme assay.

So regarding function in respect to the disclosure of NAKAWAGA, it could well be that the gene they inferred from the genome sequence could have a different function than deaminating L-serine, or it could even be that the gene was a pseudogene, that means fully inactive, without function.

Applicants do not know of any other disclosure in addition to NAKAWAGA which gives additional information about the function of the protein disclosed in new state of the art cited by the Examiner. But Applicants would like to emphasize that NAKAWAGA did not isolate the gene as assumed by the Examiner!

Thus Applicants were the first who identified the function of the gene and the correspondent protein. This means that Applicants were the first who found the main degradation path of L-serine.

KUBOTA disclosed an undirected mutagenesis to upgrade the formation of L-serine.

KUBOTA obtained a final concentration of L-serine of about 13.9 g/l. See the penultimate line of the abstract. LOVINGER did not disclose any data for L-serine formation so there is no teaching in respect to upgrade the L-serine formation by LOVINGER.

Contrary to anything disclosed in KUBOTA or LOVINGER, Applicants disclose in the present application that the L-serine dehydratase activity is unexpectedly, completely switched off when position 506 to 918 of the gene of L-serine dehydratase was deleted. This complete absence of L-serine dehydratase activity is disclosed in Table 2 page 31 of the specification in C. Glutamicum Strain 13032 ΔsdaA pXMJ19 transformed by such a form of L-serine dehydratase missing nucleotides 506 to 918. It is rather surprising that only a deletion of this part of the gene of L-serine dehydratase results in a complete deactivation of the protein. For this reason the subject matter of present claim 26 and especially claim 27 is especially believed to be surprising and unobvious, and therefore patentable over the prior art.

The complete deactivation of serine dehydratase in Applicants' approach led to a surprisingly high L-serine

accumulation of 35.7 gl. (340 mM) as published by Applicants in Applied and Environmental Microbiology 2007 (73) 750-755 (Fig. 4), by Stolz, Peters-Wendisch, Etterich, Gerharz, Faurie, Sahm, Fersterra and Eggeling, a copy of which is enclosed herewith. Should the Examiner so request Applicants are willing to make these data of record in a Declaration Under 37 CFR 1.132. Once again, . KUBOTA, according to the abstract on the first page, obtained in his approach a final L-serine concentration of 13.9 g/I, a far lower concentration.

Since Applicants' deletion of only a part of the L-serine dehydratase gene according to present claims 26 and 27 results in a higher yield of L-serine than the L-serine yield as disclosed by KUBOTA using undirected mutagenesis, then one would reasonably expect that a complete deletion of the L-serine dehydratase gene will also result in a surprisingly better yield of L-serine than the L-serine yield as disclosed by KUBOTA. Thus the remaining claims, and especially new claim 28 are believed to be patentable over the cited prior art.

There is no correlation drawn between SEQ ID NO: 141 and SEQ ID NO: 142 disclosed in WO 01/00843, cited in the International Search Report and the International Preliminary Examination Report carried out by the European Patent Office in the corresponding European Phase of the instant PCT application, and the enzymatic activity of L-serine dehydratase. Copies of the both the International Search Report and the International Preliminary Examination Report have been made of record in the present

application. Furthermore, there is also no correlation drawn between SEQ ID NO: 141 and SEQ ID NO: 142 disclosed in WO 01/00843 to L-serine degradation.

In respect to patentability over the cited prior art, Applicants maintain the following:
KUBOTA is the closest prior art to be considered, because KUBOTA teaches that L-serine dehydratase catalyzes the degradation of L-serine. It is disclosed by KUBOTA in the abstract that the L-serine concentration can be increased to 13.9 g/I through mutagenic techniques. This is a result of an undirected mutagenesis of cells of Corynebacterium glycinophilum. Mutated cells of C. glycinophilum turned out to have somewhat reduced serine dehydratase activity. There is no teaching about a direct method to influence or even to exclude degradation of L-serine by L-serine dehydratase. Thus even after KUBOTA, the problem remains to find a method and substances which allow a complete prevention of L-serine degradation.

Applicants have solved this problem by preparing the recombinant nucleic acid according to claims 1and 26 and the claims dependent thereon, and a microorganism as claimed in claim 14 . In a special feature of the invention according to claim 27, a deletion of position 506 to 918 of the nucleic acid results in aa complete prevention of the L-serine degradation by L-serine dehydratase. In another special feature of the present invention, according to claim 28, a complete deletion of the polynucleotide

expressing L-serine dehydratase results also in a complete prevention of L-serine dehydratase activity.

In KUBOTA there is no disclosure or suggestion of how to completely eliminate the activity of L-serine dehydratase and how to completely prevent the degradation of L-serine. There is in fact no disclosure of the polynucleotide which is responsible for the degradation of L-serine.

LOVINGER does not disclose a quantitative result in which activity of L-serine dehydratase is decreased. There is also in LOVINGER no disclosure of the nucleic acids which are responsible for the degradation of L-serine. With both KUBOTA and LOVINGER in hand, one "skilled in the art" would be unable to develop strains and methodology to increase L-serine formation using Corynebacterium as the source of the L-serine biosynthesase by achieving a reduced degradation of the L-serine produced by completely eliminating degradation of the L-serine by the activity of L-serine dehydratase.

Neither KUBOTA nor LOVINGER nor the combination thereof discloses or suggests that the polynucleotide according to SEQ ID NO: 1 is responsible for expressing the L-serine dehydratase that catalyzes the degradation mechanism for degrading L-serine to pyruvate.

Thus the presently claimed invention is both novel and unobvious over the combination of KUBOTA and LOVINGER..

Regarding WO 01/00843 there is no disclosure of a function of the disclosed sequences. Indeed Table 1 of the

reference shows the sequences that express L-serine dehydratase. But this is just a result of sequence comparison via computer. The real function of a polynucleotide can only be identified by experiments testing the activity of the enzyme encoded thereby, as in an enzyme assay. WO 01/00843 discloses only the result of a genome sequence determination approach and no single gene was isolated or its activity assayed. Because of this, there is no teaching in WO 01/00843 about applicability of the disclosed sequences for reducing or eliminating L-serine dehydratase activity which is the result of experiences. Thus a deletion of a particular fragment of the L-serine deyhdratase gene, especially positions 506 to 918, or even the entire L-serine dehydratase gene, as presently claimed, is both novel and unobvious over any combination of KUBOTA, LOVINGER, WO 01/00843, and/or NAKAGAWA.

NAKAGAWA was the first to publish the serine dehydratase sequence of Corynebacterium glutamicum. This is as assumed identical to serine deaminase, a term used also for the same enzyme. However, NAKAGAWA did not isolate the serine dehydratase gene. NAKAGAWA determined the genome sequence of C. glutamicum, and among the 3009 genes found they found one which they termed serine deaminase. They have neither cloned that gene, nor identified its function in an enzyme assay, nor used its sequence to derive an L-serine producer. Rather the denomination as a L-serine dehydratase (or deaminase) was just a result of comparison with a computer with other known sequences. Because of this there was no teaching about the function of the gene and the corresponding

protein because real function can only be identified by experiments testing the activity of the enzyme encoded by the gene, as in an enzyme assay.

So regarding function in respect to the disclosure of NAKAWAGA, it could well be that the gene whose sequence they inferred from the genome sequence could have a different function than deaminating L-serine, or it could even be that the gene was a pseudogene gene, that means fully inactive, without function. This situation is completely analogous to the disclosure of WO 01/00843. So the person "skilled in the art would not be motivated to delete the gene encoding for "L-serine dehydratase" as disclosed by NAKAWAGA because the real function can only be identified by the experiments testing the activity of the enzyme encoded by the gene, as in an enzyme assay.

Because there is no teaching about the function of the gene disclosed by NAKAWAGA, there is an inventive step over the combination of KUBOTA, LOVINGER, NAKAWAGA and WO 01/00843. Once again, it was especially surprising that a deletion of only the nucleotides in position 506 to 918 of the L-serine dehydratase gene results in an complete inactivation of the L-serine according to claims 26 and 27.

Applicants believe that all claims now presented are allowable over the cited prior art and a response to that effect is earnestly solicited.

Respectfully submitted,
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Enclosures:
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